# Risks of inflammatory bowel disease treatment with glucocorticosteroids and aminosalicylates

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Abstract: BACKGROUND: Glucocorticosteroids and aminosalicylates, mainly mesalazine (5-ASA), are both standard therapeutics in the treatment of inflammatory bowel disease (IBD) patients. The glucocorticosteroids are highly effective in inducing remission in both ulcerative colitis and Crohn's disease, but their use is limited by the high incidence and the potentially serious nature of adverse events. In an attempt to limit systemic side effects, rapidly metabolized corticosteroids such as budesonide have been introduced. The safety profile of aminosalicylates differs between the formulations. METHODS: We summarize the potential risks associated with glucocorticosteroid and aminosalicylate therapy in IBDs. RESULTS: The numerous adverse events of glucocorticosteroids, particularly at high doses and prolonged treatment, include opportunistic infections, diabetes mellitus, hypertension, ocular effects (glaucoma and cataracts), psychiatric complications, hypothalamic-pituitary-adrenal axis suppression and increased fracture risk. Partially, these systemic adverse events occur with budesonide, which only has a low systemic exposure. The safety profile of 5-ASA is comparable to placebo and superior to the old aminosalicylate prodrug sulfasalazine, which had a significantly higher incidence of intolerance reactions including allergic rashes. Only in rare cases has nephrotoxicity such as interstitial nephritis been associated with 5-ASA. CONCLUSION: Considering the toxicity profile of conventional glucocorticosteroids, one primary goal of treatment in IBD should be corticosteroid-free remission. Therapy with budesonide may result in a better safety profile. 5-ASA treatment is usually well tolerated, but with regard to the rare nephrotoxic events, it is advisable to assess renal function before and during treatment with 5-ASA.

DOI: https://doi.org/10.1159/000354699

Adverse Events

Digestive Diseases

Dig Dis 2013;31:368–373
DOI: 10.1159/000354699

# Risks of Inflammatory Bowel Disease Treatment with Glucocorticosteroids and Aminosalicylates

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**Key Words**
Glucocorticosteroids · Mesalazine · Inflammatory bowel disease · Adverse events

**Abstract**
***Background:*** Glucocorticosteroids and aminosalicylates, mainly mesalazine (5-ASA), are both standard therapeutics in the treatment of inflammatory bowel disease (IBD) patients. The glucocorticosteroids are highly effective in inducing remission in both ulcerative colitis and Crohn's disease, but their use is limited by the high incidence and the potentially serious nature of adverse events. In an attempt to limit systemic side effects, rapidly metabolized corticosteroids such as budesonide have been introduced. The safety profile of aminosalicylates differs between the formulations. ***Methods:*** We summarize the potential risks associated with glucocorticosteroid and aminosalicylate therapy in IBDs. ***Results:*** The numerous adverse events of glucocorticosteroids, particularly at high doses and prolonged treatment, include opportunistic infections, diabetes mellitus, hypertension, ocular effects (glaucoma and cataracts), psychiatric complications, hypothalamic-pituitary-adrenal axis suppression and increased fracture risk. Partially, these systemic adverse events occur with budesonide, which only has a low systemic exposure. The safety profile of 5-ASA is comparable to placebo and superior to the old aminosalicylate prodrug sulfasalazine, which had a significantly higher incidence of intolerance reactions including allergic rashes. Only in rare cases has nephrotoxicity such as interstitial nephritis been associated with 5-ASA. ***Conclusion:*** Considering the toxicity profile of conventional glucocorticosteroids, one primary goal of treatment in IBD should be corticosteroid-free remission. Therapy with budesonide may result in a better safety profile. 5-ASA treatment is usually well tolerated, but with regard to the rare nephrotoxic events, it is advisable to assess renal function before and during treatment with 5-ASA.



## Glucocorticosteroids

### *Introduction*

Systemic glucocorticoids are effective at inducing remission in both ulcerative colitis (UC) and Crohn's disease (CD) [1–4], whereas they are ineffective in the maintenance of remission in either illness [5]. However, their use is limited by their frequent, various and sometimes serious side effects: the most frequent and most typical side effects concern the skin, such as thinning of the skin

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or purpura. Steroids affect bone and can induce both osteonecrosis and osteoporosis [6]. They increase susceptibility to various fungal, viral and bacterial infections [7]. Myopathy is an infrequent complication, typically presenting as proximal weakness of both the upper and lower extremities and sometimes with atrophy and paresis [8]. Furthermore, steroids predispose to a range of psychiatric complications such as depression, insomnia or euphoria [9]. Cushingoid features with weight gain and redistribution of body fat are often quite troubling to the patients. Besides, a relevant proportion of patients develop hyperglycemia. Especially if glucocorticosteroids are used in combination with nonsteroidal anti-inflammatory drugs, the risk for peptic ulcer disease is significantly increased. The impact of glucocorticosteroids on atherosclerotic disease is supposed to be partly mediated by changes in lipoprotein levels [10]. Ophthalmologic adverse effects include both glaucoma and cataract (posterior subcapsular cataracts are typical). Finally, if systemic glucocorticoids are stopped without adequate tapering, adrenal insufficiency may develop.

In order to limit systemic toxicity, novel steroids with limited oral bioavailability such as the second-generation glucocorticosteroid budesonide have been developed as an alternative to classic corticosteroids. Budesonide exerts its local effects due to its high affinity to the glucocorticoid receptor, which is approximately 200 times that of prednisolone [11]. Budesonide has a limited systemic bioavailability of only 10–15% due to extensive first-pass metabolism by cytochrome P-450 enzymes. But, potent CYP3A4 inhibitors such as macrolide antibiotics (clarithromycin, erythromycin) or azole antifungals (ketoconazole, itraconazole) can increase plasma concentrations to a relevant extent [12, 13] and consequently may increase the risk for systemic budesonide-associated side effects.

*Budesonide and Systemic Adverse Events*

Despite its low oral bioavailability, adverse events were more common in CD patients treated with 6 mg budesonide daily for maintenance of remission than with placebo according to a recent Cochrane analysis (RR 1.49; 95% CI 1.01–2.19) [14], but adverse events were usually mild and did not result in increased rates of study withdrawal. On the contrary, compared with conventional corticosteroids used for the induction of remission in CD, patients who received budesonide had significantly less systemic side effects (RR 0.64; 95% CI 0.54–0.76) [15]. Abnormal responses to ACTH tests were significantly more common in budesonide-treated patients (both 3 and 6 mg) than in those who received placebo (RR 2.73; 95% CI 1.34–5.57 and RR 2.88; 95% CI 1.72–4.82) [15] but less common than in patients who received conventional glucocorticosteroids for the induction of remission in CD (RR 0.65; 95% CI 0.55–0.78) [15].

*Glucocorticosteroids and Hyperglycemia*

Glucocorticosteroids are the most common cause of drug-induced diabetes mellitus. More than 50% of patients who receive glucocorticosteroids at a dose equivalent of 40 mg prednisolone or more per day develop hyperglycemia [16, 17]. The odds ratio for the development of a new-onset diabetes mellitus is 1.36–2.31 [18]. Predisposing factors are a family history of diabetes, a hospitalization in the preceding 4 months, a preexisting glucose intolerance, obesity, higher age and most importantly dose and duration of glucocorticoid therapy. Glucocorticosteroids induce hyperglycemia mainly through increased insulin resistance. Typically, postprandial glucose is elevated while fasting glucose concentrations are often normal if glucocorticosteroids are administered once daily. It is recommended to monitor random plasma glucose, typically in the afternoon or 1–2 h postprandially. There are currently no published guidelines for the monitoring of plasma glucose in patients with inflammatory bowel disease (IBD) with glucocorticosteroid therapy, but at least at the start of therapy, it may be advisable to check glucose not less than once weekly in patients who receive high doses of corticosteroids and who have no or only few risk factors for the development of steroid-induced diabetes. In patients with several risk factors, glucose concentrations should be tested at least once weekly. To treat hyperglycemia, oral antidiabetics such as metformin or sulfonylureas may be used if glucose concentrations are <12–15 mmol/l. If concentrations are higher, insulin therapy should be started. Longer-acting NPH insulin has a similar action profile to prednisone and prednisolone and can be given once daily in the morning. Therefore, NPH insulin can serve as a simple alternative for prandial insulin therapy.

*Hypothalamus-Pituitary-Adrenal Axis*

Already 5 days of treatment with higher doses of glucocorticoids (>25 mg/day prednisone or equivalent) induce at least a partial suppression of the hypothalamus-pituitary-adrenal (HPA) axis in 40% of patients [19]. Whether this is clinically relevant is dependent on the individual stress level of the patient, such as trauma, acute infection or critical illness. In order to avoid both cortisol deficiency and acute flare-up of disease, careful tapering

of the glucocorticoid dose is mandatory. To date, there is no published 'gold standard' for tapering of glucocorticosteroids in IBD patients and several possible regimes exist. One approach is to decrease prednisone/prednisolone dose by 5 mg weekly until a daily dose of 20 mg is achieved. Below 20 mg, the dose is tapered by 2.5 mg (to 5 mg) weekly, until therapy is stopped. HPA axis function testing is ideal 1 day after finishing steroid therapy, but, in exceptional cases (e.g. if the dose cannot be reduced any further), it may be performed at prednisone doses ≤5 mg. A simple test for measuring HPA function is the ACTH stimulation test. Two types exist, the 'classical' (Synacthen®) test with 250 μg corticotropin given intravenously and the low-dose test with 1 μg corticotropin given intravenously. Several studies have concluded that the low-dose test is slightly more sensitive than the classical test for detecting secondary adrenal insufficiency [20–22]. The stimulated cortisol level is considered normal >500 nmol/l (18 mg/dl).

*Infection Risk*

Glucocorticosteroid therapy predisposes to infections and several studies have evaluated the risk of infectious complications in IBD patients treated with corticosteroids. According to a TREAT registry (Crohn's Therapy Resource, Evaluation, and Assessment Tool registry) analysis that compared infliximab safety with nonbiological drug therapy, prednisone therapy was independently associated with serious infections (HR 1.57; 95% CI 1.17–2.10) and also with an increased mortality risk (HR 2.14; 95% CI 1.55–2.95) [23]. In a case-control study in 100 IBD patients with opportunistic infections, glucocorticosteroids alone yielded an OR of 2.2 (95% CI 1.0–4.9) after multivariate analysis, whereas infection risk further increased with the number of immunosuppressives (OR 14.5; 95% CI 4.9–43.0 for 2 or 3 drugs) [24]. Glucocorticosteroid therapy in IBD patients undergoing elective bowel surgery significantly increased postoperative infection risk according to a retrospective cohort study (OR 3.69, 95% CI 1.24–10.97 for any infectious complications) [25]. According to another case-control study, glucocorticosteroids were the only independent risk factor for infections in infliximab-treated patients (OR 2.69; 95% CI 1.18–6.12) [26].

*Effects on Bone*

The prevalence of osteoporosis (with a T score <–2.5) in IBD patients is high, ranging from 18 to 42% in clinical studies, whereas the reported prevalence rates of osteopenia are even higher (22–77%) [27–29]. The main factors contributing to the development of osteoporosis in IBD patients are disease activity and glucocorticosteroid use, but since these are closely linked, it is difficult to differentiate between both factors in terms of impact on bone loss. Glucocorticosteroids increase bone resorption and bone remodeling rate early after starting therapy and also reduce bone formation. Factors contributing to glucocorticoid-induced bone loss are the suppression of osteoclast-inhibiting factors such as osteoprotegerin and the induction of the formation of osteoclastogenic factors, such as receptor activator of nuclear factor-κB ligand [30]. Bone loss and fracture risk increase rapidly (in the first 3–6 months) after initiation of therapy and are dose-dependent. Interestingly, an increase in fracture risk has already been demonstrated with doses as low as 2.5–7.5 mg prednisone daily and not only with doses exceeding 7.5 mg daily [31]. The greatest risk is seen for vertebral fractures [31]. Upon cessation of glucocorticosteroid therapy, fracture risk rapidly declines [31]. Data evaluating oral budesonide effects on bone is sparse, but in one trial corticosteroid-naive CD patients treated with budesonide showed better preserved bone mineral density than those treated with prednisolone [32]. Intervention thresholds for the management of glucocorticoid-induced bone loss vary among countries and among different societies, but in general, treatment should be considered in patients exposed to systemic glucocorticosteroids ≥3 months [33–35]. Bisphosphonates are still the treatment of choice.

## Aminosalicylates

*Introduction*

Aminosalicylates have been used in the treatment of IBDs for more than 60 years now. They are established therapies for inducing and maintaining remission in UC [36, 37], whereas their efficacy is not proven in the treatment of CD [5, 38]. A recent Cochrane review suggests that mesalazine (5-aminosalicylic acid, 5-ASA) is not effective in maintaining medically-induced remission in CD [39]. Aminosalicylates chemically originate from sulfasalazine, which was initially developed for the treatment of rheumatologic diseases in the 1940s. Sulfasalazine is split by bacterial azoreductase in the colon into the inactive sulfapyridine and the therapeutic mesalazine moiety. The discovery that 5-ASA is the active part of sulfasalazine was followed by the development of many different 5-ASA formulations (oral, rectal, pH-independent continuous release, pH-dependent release, multimatrix technology) allowing release in both the colon and/or

small intestine. Meanwhile, several aminosalicylates (sulfasalazine, olsalazine, balsalazide and mesalazine) are available for use in IBDs, but in the USA more than 88% of patients receive 5-ASA [40, 41]. The mechanism of action of 5-ASA in UC is complex and several effects have been observed [42]. It is believed that 5-ASA interacts with damaged epithelium and mediates its effect locally on the mucosa. 5-ASA is a scavenger of reactive oxygen metabolites and inhibits leukocyte chemotaxis [43]. Besides, 5-ASA targets several intracellular pathways leading to changes in gene regulation: tumor necrosis factor-α/nuclear factor-κB, transforming growth factor-β, interleukin-1 and epidermal growth factor signaling, protein synthesis and Wnt/b-catenin signaling, peroxisome proliferator-activated receptor-γ and apoptosis [44–46].

*Adverse Events*

Compared to 5-ASA, side effects occur more often with sulfasalazine therapy, with an adverse event rate ranging from 10 to 45%, depending on the sulfasalazine dose [47–49]. Frequent adverse effects are headache, nausea, epigastric pain or rash. Several adverse effects like hypersensitivity reactions were attributed to the inactive sulfapyridine moiety, which is absorbed from the colon. Slow acetylator genotype of N-acetyltransferase-2 may predispose to sulfasalazine-associated adverse effects [50–52]. Some of the rare, but potentially serious adverse effects are blood dyscrasias like agranulocytosis [53], alveolitis [54, 55] and pancreatitis [56]. In contrast, 5-ASA therapy is well tolerated and the adverse event rate of 5-ASA (e.g. gastrointestinal disturbances such as abdominal pain, flatulence, nausea, dyspepsia) is 5%, which is similar to placebo according to several randomized controlled clinical trials [57, 58]. The incidence of intolerance reactions is significantly lower than with sulfasalazine therapy. Besides, according to a recent Cochrane review [58], high 5-ASA doses are not associated with a higher incidence of adverse effects and are as safe as low doses.

*Nephrotoxicity*

Numerous cases of nephrotoxicity have been described for 5-ASA therapy [59–64]. Nevertheless, several studies evaluating the effect of 5-ASA on renal function conclude that nephrotoxicity is a rare event: according to data from an adverse event monitoring in the United Kingdom, interstitial nephritis was reported in 11.1 per 1 million 5-ASA prescriptions [65]. In a retrospective survey in patients with CD, long-term 5-ASA use led to a mean decline in glomerular filtration rate of 0.3 ml/min/year which did not exceed the decline expected from physiologic aging [66]. In a large epidemiologic study the incidence rate of renal disease was higher in IBD patients without 5-ASA therapy (0.25/100 patients per year) compared to those with 5-ASA use (0.17/100 patients per year) [67]. According to an analysis from a postal questionnaire (United Kingdom) the incidence of nephrotoxicity was estimated at 1/4,000 patients per year in 5-ASA users [68]. 5-ASA-related nephrotoxicity typically presents as interstitial nephritis, which often occurs in the first 12 months of therapy [69], but can potentially occur at any time. If detected early, interstitial nephritis seems to be reversible [63, 64]. Currently, there are no established monitoring guidelines, but it may be advisable to check renal function before and every 3–6 months during aminosalicylate therapy.

## Disclosure Statement

The authors have no conflicts of interest to disclose.

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